# Study of Prefrontal Cortical Metabolism in Stressed and Resilient Mice in Social Defeat Model of Depression

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**INTRODUCTION:** Major depressive disorder (MDD) is a complex neuropsychiatric syndrome, often very severe and life threatening. Clinical evidence suggests that the glutamatergic system plays an important role in the pathophysiology of MDD[1]. GABAergic deficit in depressive disorders is based on reduced GABA levels in plasma, cerebrospinal fluid and in cortical tissue of depressed patients[2]. Although there are strong reasons to believe that abnormalities in MDD are associated with glutamatergic and GABAergic system, the mechanisms responsible for the abnormal Glu and GABA level in the brain of depressed patients are still not clear. We hypothesized that depression like phenotype induced by repeated social defeat events will reduce the energetics of glutamatergic and GABAergic pathways. In this study, we have investigated cerebral metabolism in prefrontal cortex in depressed and resilient mice subjected to psychosocial defeat paradigm by using $^{1}$H-[$^{13}$C]-NMR spectroscopy.

**MATERIALS AND METHODS:** All the animal experiments were performed under protocols approved by the Institute Animal Ethics Committee. Two groups of two month old male C57BL/6 mice were used: Group (i) social defeat (n=7), Group (ii) control (n=3). Group (i) mice were subjected to social defeat paradigm of 5 min a day for 10 days with aggressive CD1 mice. Mice were evaluated for depression like phenotype by sucrose preference test and social interaction test. Mice showing significant behavioral changes were treated as depressed (n=4) while those showing no change were treated as resilient (n=3). For metabolic study, overnight fasted mice were anesthetized with urethane (1.5 g/kg, i.p.) and [1,6-$^{13}C_2$]glucose was administered (i.v.) for 10 min[3]. Metabolites were extracted from frozen prefrontal cortical tissue[4]. Concentration and percent $^{13}$C enrichment of metabolites were determined from the $^{1}$H-[$^{13}$C]-NMR spectrum of the extract recorded at 600 MHz NMR spectrometer (Bruker AVANCE II)[5].

**RESULTS AND DISCUSSIONS:** Level of glutamate, aspartate, taurine and choline was found to be decreased ($p<0.05$) in prefrontal cortex of depressed mice (Fig. 1). Resilient mice showed increase in GABA (2.7±0.3 vs. 3.7±0.3 µmol/g, $p=0.04$, n=3,3) level without significant change in other metabolites. Metabolic investigations showed reduction ($p<0.04$) in the $^{13}$C labeling of $Glu_{C4}$ and $GABA_{C2}$ from [1,6-$^{13}C_2$]glucose in depressed mice while resilient displayed reduction ($P<0.04$) in $GABA_{C2}$ only (Fig. 2). These data suggest depression like symptoms are associated with reduced glutamatergic and GABAergic activity. Increased GABA level together with unperturbed glutamatergic function in resilient mice might be rescuing them from depression.

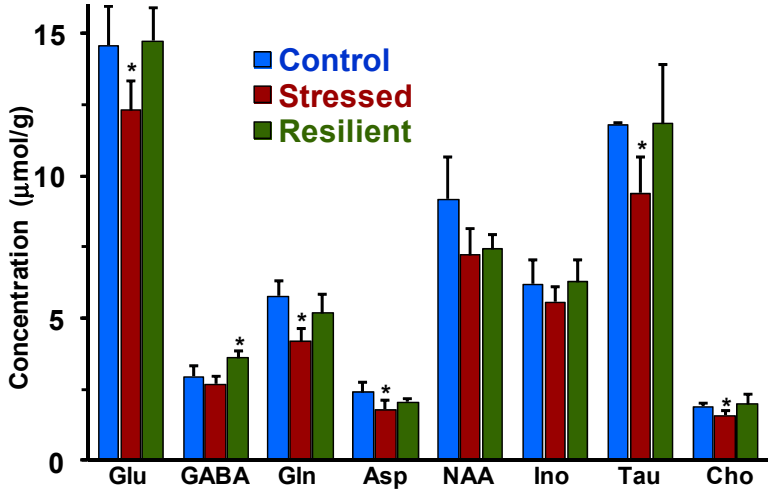


**Fig. 1 Concentration of neurometabolites in prefrontal cortex of mice after social defeat**

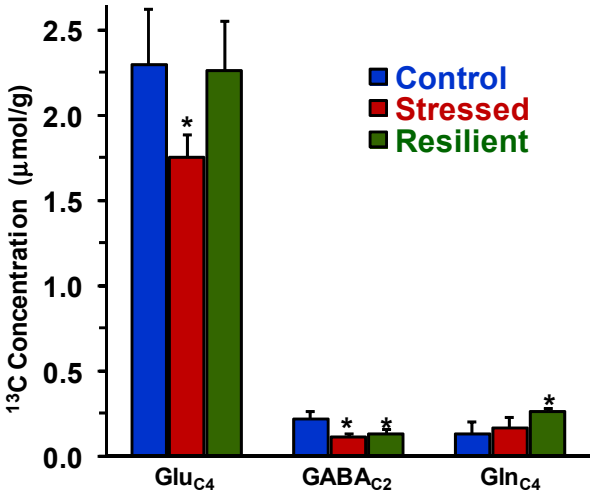


**Fig. 2 Concentration of $^{13}$C labeled amino acids in prefrontal cortex of mice after social defeat**

**REFERENCES:** 1. Sanacora et al (2008) *Nat Rev Drug Discov* **7**:426; 2 Honig et al (1988) *J Psychiatr Res* **22**:159; 3. Fitzpatrick et al (1990) J *Cerb Blood Flow Metab* **10**:170; 4. Patel et al (2001) *Brain Res* **919**:207; 5. De Graaf *et al* (2003) *Magn Reson Med* **49**:37.

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